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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/625,100	07/22/2003	Santiago Munne		8781

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/625,100	MUNNE, SANTIAGO	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-4 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-4 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 7/22/03.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-4 are pending and under current examination.

Claim Objections

Claims 1-3 are objected to because of the following informalities:

1. The claims do not start with a sentence "I (or we) claim, " or "The claimed invention is" (or the equivalent). See MPEP §608.01 (m).

2. Claims 1 and 2 do not end in a period.

3. Claim 3 has multiple periods (see parts a, b, and e). Each claim should begin with a capital letter and end with a period. Periods may not be used elsewhere in the claims other than for abbreviations. See MPEP §608.01 (m) and *Fressola v. Manbeck,* 36 USPQ2d 1211 (D.D.C. 1995).

4. Claim 3 sets forth a plurality of elements or steps but they are not separated by a line indentation (see also, 37 CFR 1.75 (i)). Particularly, part e) of the claim has two steps (fixing and analysis by FISH) and then Identifying and Isolating. It is suggested that the identification and isolation step be amended to be step f).

5. The claim numbering is objected to, they are not appropriately numbered as c1, c2, etc. It is suggested to number the claims as 1.; 2. etc.

Appropriate correction is required.

Information Disclosure Statement

Applicants' IDS, filed 7/22/03, has been considered.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

The citizenship of the inventor is designated as "American". This is unclear (it encompasses North, South and Central America). If the citizenship of the inventor is from the United States, Applicants are requested to change this to "United States."

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of producing disomic human embryonic cell lines by culturing trisomic human embryos onto mouse feeder cells, consisting of mouse embryonic fibroblast cells, wherein the mouse embryonic fibroblast cells have been previously been mitotically inactivated by mitomycin C in gelatin-tissue culture dishes, maintain said mouse feeder cells using DMEM as claimed, supplementing the medium with human LIF, culturing the embryos in said medium until day 12, fixing and analyzing said embryonic cell lines, identifying and isolating disomic cell lines within said embryonic cell lines wherein disomic cell lines are produced, does not reasonably provide enablement for the production of embryonic stem cell lines, or stem cell lines using the claimed methods. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the

art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention/Breadth of the claims. The invention is directed to methods of producing disomic human embryonic cell lines by culturing trisomic human embryos onto mouse feeder cells, consisting of mouse embryonic fibroblast cells, wherein the mouse embryonic fibroblast cells have been previously been mitotically inactivated by mitomycin C in gelatin-tissue culture dishes, maintain said mouse feeder cells using DMEM as claimed, supplementing the medium with human LIF, culturing the embryos in said medium until day 12, fixing and analyzing said embryonic cell lines, identifying and isolating disomic cell lines within said embryonic cell lines wherein disomic cell lines are produced.

Guidance of the Specification/The Existence of Working Examples. The specification teaches chromosomally abnormal human embryos were cultured in sequential media, and the trophectoderm of the hatching blastocyst were biopsied to confirm chromosomal abnormality. The specification teaches that the remainder of the embryo was then plated on mouse embryonic fibroblast feeder layers. The embryos were then cultured until day 12, where the human cells were fixed and analyzed by FISH. A progressive increase from abnormal to normal cells was found between day 6 and day 12, and that by day 12, all 7 cultured embryos were mosaics. The specification teaches that this observed reduction in trisomic cells cannot be due to the non-survival of trisomic embryos in culture, and that the most reasonable explanation is that the trisomic cells revert to disomic cells in extended culture. See pages 3-4 of the specification and Table 1 (page 6). The specification teaches that this method can be used to obtain chromosomally normal stem cells from trisomic embryos. The specification provides a prophetic example of how to derive a

disomic cell line from these cells (see pp. 6-7, Method for derivation of single-cell clones).

State of the Art/Predictability of the Art. The breadth of the claims encompasses embryonic stem cells, which would be pluripotent and exhibit characteristics of embryonic stem cells. For example, Thomson *et al.* (**PNAS**, 92:7844-7848 (August 1995)) teach the specific, art-recognized characteristics of pluripotent cells - that these cells remain undifferentiated in culture in continuous passage, maintain a normal karyotype, express appropriate cell markers [alkaline phosphatase, SSEA-3, SSEA-4, TRA-160-, TRA-1-81] and, when injected into SCID mice, they consistently differentiate into derivatives of all three germ layers. See *Abstract* and p. 7845-7846. Although the specification provides guidance to show that embryonic cells can be produced, using the claimed methods, there is no guidance with regard to the particular markers expressed by these cells, or that these cells have differentiation potential of pluripotent cells. The specification is only directed to the karyotypic analysis of the embryonic cells (see Table 1). There is no guidance to show the isolation of inner cell mass cell from the embryos, and the subsequent analysis of the cells to show that they would indeed show the characteristics of embryonic stem cells. Indeed, the specification states that in the initial study, trophectoderm and inner cell mass cells were not independently fixed for further FISH analysis (see paragraph 13, page 4). Furthermore, the specification clearly states that the yield of disomic cells from the chromosomally abnormal embryos is extremely low, as only 7/44 embryos developed in culture until day 12. See p. 5, paragraph 18.

The Amount of Experimentation Necessary. Accordingly, in view of the state of the art of embryonic stem cells, namely the specific, art-recognized characteristics of such cells, the lack of teaching, guidance or characterization of cells produced by the claimed method, other than karytotypic analysis of the cells, the unpredictable state of the art of producing embryonic stem cells,

and the lack of guidance or teaching provided by the specification to overcome these unpredictibilities, it would have required undue experimentation for one of skill in the art to make and use the claimed disomic cell lines.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 2 are rejected under 35 U.S.C. 102 (b) as being anticipated by Thomson [WO 96/22362, published 25 July 1996].

The claims are directed to a disomic cell line derived from trisomic embryos, and a stem cell line derived from disomic cell lines.

Note that the claims are product-by-process claims. Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke, supra. Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). Further, see MPEP §2113, "Even though product-by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process."

Thomson teach the isolation and purification of primate embryonic stem cells that are capable of indefinite proliferation *in vitro* in an undifferentiated state, are capable of differentiation to derivatives of all three embryonic germ layers, and maintain a normal karyotype throughout prolonged culture. The pluripotent cells are negative for SSEA-1, positive for the SSEA-3 marker, positive for the SSEA-4 marker, TRA-1-60, TRA-1-81 and alkaline phosphatase. Thomson teach that the primate cells can continue to proliferate in an undifferentiated state for at least one year. See p. 7, lines 9-32. Thomson teach that tumors formed after injection of rhesus ES cells into the hindleg muscles of SCID mice [see Figure 5].

Accordingly, Thomson *et al.* anticipate the claimed invention.

Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Shamblott *et al.* [**PNAS**, 95:13726-13731 (1998)].

The claims are directed to a disomic cell line derived from trisomic embryos, and a stem cell line derived from disomic cell lines.

The claims are product-by-process claims (see above). Shamblott teach that human pluripotent stem cells were isolated from gonadal ridges and mesenteries of 5- to 9-week postfertilization human embryos. Cells were cultured and subsequently passaged onto a mouse STO fibroblast feeder layer. Shamblott teach that embryoid bodies were collected from cultures and immediately embedded or replated into single wells [under conditions using mouse embryo fibroblasts, human fetal fibroblasts, or gelatin-coated tissue culture, see p. 13729, 1st column, 1st full ¶] and cultured for 14 days in the absence of hrLIF, hrbFGF and forskolin. See pp. 13726-13727, *Materials and Methods*. They teach that immunohistochemical analysis of embryoid bodies demonstrated that the cells could differentiate into a variety of cell types, including derivatives of the three embryonic germ layers. See p.

13729, 2nd column, 1st full ¶. They teach that these cellsl are karyotypically normal (see Abstract, and Material and Methods).

As Shamblott *et al.* teach human pluripotent stem cells which have a normal karyotype, they teach a disomic cell line, as required by the claims. Accordingly, Shamblott *et al.* anticipate the claimed invention.

Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Thomson *et al.* (**PNAS**, 92:7844-7848 (August 1995)).

The claims are directed to a disomic cell line derived from trisomic embryos, and a stem cell line derived from disomic cell lines.

Thomson *et al.* teach pluripotent primate embryonic stem cells, isolated from a rhesus monkey blastocyst. They teach that these cells remain undifferentiated in culture in continuous passage, maintain a normal karyotype, express appropriate cell markers [alkaline phosphatase, SSEA-3, SSEA-4, TRA-160-, TRA-1-81] and, when injected into SCID mice, they consistently differentiate into derivatives of all three germ layers. See *Abstract* and p. 7845-7846.

Accordingly, as Thomson teach a disomic stem cell line, they anticipate the claimed invention.

Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Thomson [**U.S. Pat. No.** 6,200,806 B1, March 13, 2001].

The claims are directed to a disomic cell line derived from trisomic embryos, and a stem cell line derived from disomic cell lines.

Thomson teach the preparation of a primate embryonic stem cell line that has expresses the cell surface markers characteristic of embryonic stem cells, have normal karyotypes, are able to proliferate in an undifferentiated state in continuous culture, and the ability to differentiate into all tissues derived from all three embryonic germ layers (see Abstract and claims).

Thus, because Thomson teach a karyotypically normal human embryonic stem cell line, they anticipate the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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